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Therapeutic effects and predictive factors for successful intravesical hyaluronic acid instillation in patients with interstitial cystitis/bladder pain syndrome

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ABSTRACT

Objective: Hyaluronic acid (HA) is currently used in Taiwan as intravesical instillation for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS). This study investigated the therapeutic effects of HA on IC/BPS in the Taiwanese population.

Materials and methods: Men and women aged ≥18 years with documented IC/BPS were initially treated with four weekly intravesical HA instillations (treatment time, 1 month) and then with five monthly instillations (total treatment time, 6 months). Clinical assessments included the evaluation of the Visual Analog Scale (VAS) score of bladder pain, O'Leary–Sant Symptom (OSS) score, IC Symptom Index (ICSI), IC Problem Index (ICPI), functional bladder capacity (FBC), uroflowmetry parameters, and global response assessment (GRA). Therapeutic effects were compared between responders (GRA increased ≥ 2 scales) and nonresponders (GRA increased < 2). Multivariate linear analysis was used to determine predictive factor for successful treatment.

Results: A total of 64 patients (3 men and 61 women) with mean age of 49.4 years (range, 20–79) completed the study. Compared with the baseline data, VAS, ICSI, ICPI, OSS score, daytime frequency, nocturia, and FBC all improved at 1 month or 6 months after starting HA treatment. Significantly more improvements in ICSI, ICPI, OSS score, VAS, and FBC were noted in the responders than in the non-responders at 6 months of treatment. A low-grade glomerulation was the only predictor for successful treatment response to intravesical HA treatment.

Conclusion: Intravesical HA administrations improved IC symptoms, decreased bladder pain, and decreased frequency after four instillations, and decreased nocturia and increased bladder capacity after completion of all nine instillations. Low-grade glomerulation predicts successful outcome.

1. Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic bladder condition characterized by bladder pain, urination frequency, and nocturia. Many different etiologies have been proposed; however, none of these etiologies has been definitively proven. Therefore, no single treatment has been reported to have a long-term effect in eradicating symptoms of this mysterious bladder disorder.[1] IC/BPS is considered to result from long-standing inflammation of the bladder. Histological analyses of the bladder show infiltrates of mast cells, eosinophilic leukocytes, and T lymphocytes, suggesting that the disease is mediated by the immune system.[2]

Previous reports indicated that the urothelium plays a pivotal role as a barrier between urine and its solutes and the underlying bladder. Bladder surface mucus is a critical component of this function.[3–5] In patients with IC/BPS, disruption of the urothelial barrier may initiate a cascade of events in the bladder, leading to symptoms and disease. Specifically, urothelial dysfunction leads to the migration of urinary solutes, in particular, potassium that depolarizes nerves and muscles and causes tissue injury.[6,7] Consequently, it is imperative to understand the biological effects by which the urothelium changes its growth behavior and the expression patterns of signal transduction molecules under these effects.

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Previously published results and data support the notion that IC/BPS involves an aberrant differentiation program in the bladder urothelium that leads to altered synthesis of several proteoglycans, cell adhesion and tight junction proteins, and bacterial defense molecules (e.g., GP51).[8] Therefore, replacement therapy with glycosaminoglycan has been widely used for treatment of IC/BPS. Hyaluronic acid (HA) is a nonsulfated mucopolysaccharide component of the glycosaminoglycan layer and is present in the subepithelial connective tissue to protect the bladder wall from irritants in the urine.[9,10] Intravesical treatment with this agent has been investigated in IC/BPS patients. Morales et al[10] treated 25 IC patients with 40-mg HA weekly for 4 weeks and then monthly. They reported an initial positive response rate of 56% at Week 4. When the patients were evaluated at Week 12, the response rate increased to 71%. This positive response rate was maintained until Week 20, but decreased after Week 24.[10] Recent studies also confirmed that intravesical instillation of HA can provide both immediate and sustained relief of symptoms. Although various treatment modalities of HA are available, including adding alkalinized lidocaine,[11] instillation of HA through electromotive drug administration,[12] or biweekly intravesical instillations,[13] the therapeutic efficacy of all these modalities seems consistently satisfactory.

HA has been used in treatments in Taiwan since 2007. At present, HA is the most popular first-line treatment for cystoscopy-proven IC/BPS. This study investigated the therapeutic results and the predictive factors of IC/BPS patients treated with intravesical HA instillations in Taiwan.

2. Methods

This was a prospective clinical study. A total of 90 men and women (age $\geq$ 18 years) with documented IC/BPS were selected for HA treatment. All patients had the characteristics of IC/BPS and were previously treated conservatively with heparin and/or pentosan polysulfate and were refractory to treatment.[14] All patients underwent urodynamic studies with 0.4 M potassium chloride (KCl) prior to cystoscopic hydrodistention. The patients underwent cystoscopic hydrodistention at an intravesical pressure of 80 cm of water and were examined for glomerulations. The grade of glomerulations was classified as 0–4, indicating none, mild, moderate, and severe glomerulations, and as Hunner's lesions, respectively.[15] Patients with a cystometric bladder capacity of >350 mL or without a positive KCl test during urodynamic testing were not included in this study. Patients with urinary tract infection, stress urinary incontinence, chronic urinary retention, pelvic organ prolapse, or neurogenic voiding dysfunction were also excluded.

This study was approved by the Institutional Review Board and Ethics Committee of the Buddhist Tzu Chi General Hospital, Hualien, Taiwan and Tzu Chi University, Hualien, Taiwan. Each patient was informed about the study rationale and procedures prior to the treatment. Patients were also informed about the possible complications associated with intravesical HA instillation, such as urinary tract infection. Written informed consent was obtained from every patient prior to participation.

The patients were treated with intravesical HA (40 mg in 50 mL of solution; Cystistat, Mylan Teoranta, Galway, Ireland) instilled weekly for 4 weeks followed by monthly instillation for 5 months. The HA treatment was started 1 month after cystoscopic hydrodistention. The patients did not receive any additional treatment. Clinical assessments were performed at baseline, 1 month (after the 4th HA instillation), and 6 months (after the 9th HA instillation). The clinical assessments included symptom score, 3-day voiding diary, and uroflowmetry. The symptoms at baseline and after HA treatment were assessed using the O'Leary–Sant Symptom (OSS) score, IC Symptom Index (ICSI), IC Problem Index (ICPI),[16,17] and 10-point Pain Visual Analog Scale (VAS).[18] In addition, the 3-day voiding diary was used to assess functional bladder capacity (FBC), daily frequency and nocturia, and uroflowmetry including the maximum flow rate (Q_{max}), voided volume, and postvoid residual volume at each time point.

Treatment efficacy was analyzed based on the global response assessment (GRA).[19] Patients rated their bladder symptoms compared with baseline on a 7-point, centered scale as follows: markedly (+3), moderately (+2), or slightly improved (+1), no change (0), to slightly (−1), moderately (−2), and markedly worse (−3). Successful treatment outcomes were defined as moderately and markedly improved results after treatment.[20,21] Patients who responded to HA treatment were compared with patients who did not respond to all parameters from baseline to 1 month and 6 months after starting HA treatment.

Continuous variables were expressed as means ± standard deviations, and categorical data were expressed as number and percentage. Statistical comparisons between the subgroups were tested using Chi-square test for categorical variables, and the Wilcoxon rank-sum test was used for continuous variables. The Wilcoxon signed-rank test was used to evaluate the significance of differences at baseline and after treatment. Multivariate linear analysis was used to determine the predictive factor for a successful response to HA treatment at 6 months. All statistical assessments were two sided and considered significant at $p < 0.05$. Statistical analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

3. Results

A total of 90 patients were enrolled. After cystoscopic hydrodistention, 26 patients withdrew from the study due to IC/BPS symptom improvement after hydrodistention ($n = 8$), severe discomfort after the first or second HA instillation ($n = 10$), or being unable to continue HA instillations for 6 months ($n = 8$). Finally, 64 patients completed the study and were available for final analysis. The patients (3 men and 61 women) ranged in age from 20 years to 79 years (mean, 49.4 years). Cystoscopic hydrodistention revealed glomerulations of Grade 0 in three (4.7%) patients, Grade 1 in 26 (40.6%) patients, Grade 2 in 22 (34.4%) patients, Grade 3 in 10 (15.6%) patients, and Grade 4 in three (4.7%) patients. Hunner's lesion was noted in five (8%) patients.

Overall, GRA improved by $\geq$ 2 scales in 31 patients (responders, 48.4%) and by < 2 scales in 33 patients (nonresponders, 51.6%). Table 1 lists the results for all parameters measured at 1 month and

Table 1
Changes in values of urodynamic parameters at the 1- and 6-month evaluations.

	Baseline	1 mo	6 mo	*p*
VAS	4.25 ± 2.22	2.61 ± 1.87	2.33 ± 2.03	<0.001
ICSI	10.4 ± 3.73	7.41 ± 2.96	6.88 ± 3.11	<0.001
ICPI	9.63 ± 3.88	6.92 ± 3.62	5.94 ± 3.87	<0.001
OSS	20.0 ± 7.30	14.3 ± 6.15	12.8 ± 6.66	<0.001
FBC (mL)	158 ± 91.1	183 ± 88.2	214 ± 99.0	<0.001
Q_{max} (mL/s)	16.25 ± 9.56	16.87 ± 9.16	18.0 ± 10.5	0.346
Volume (mL)	227 ± 143	225 ± 137	233 ± 168	0.932
PVR (mL)	39.4 ± 48.4	36.6 ± 46.5	36.9 ± 57.6	0.920
Frequency/day	10.7 ± 5.46	8.13 ± 2.61	7.98 ± 2.88	<0.001
Nocturia/day	3.11 ± 1.61	2.44 ± 1.17	2.58 ± 1.32	0.001

FBC = functional bladder capacity; ICPI = Interstitial Cystitis Problem Index; ICSI = Interstitial Cystitis Symptom Index; OSS = O'Leary–Sant Symptom score; PVR = postvoid residual volume; Q_{max} = maximum flow rate; VAS = Visual Analog Scale of pain.

6 months after HA treatment. VAS, OSS score, ICSI, and ICPI all showed significant decrease at the 1- and 6-month assessments. Urination frequency and nocturia also decreased at the 1- and 6-month assessments. However, according to the GRA scale, moderate and marked improvements were reported in 24 (38%) patients and seven (11%) patients at the 1-month evaluation, and in 18 (28%) patients and 13 (20%) patients at the 6-month evaluation, respectively. At the 1-month evaluation, seven (11%) patients and 26 (41%) patients reported no change or mild improvement; at the 6-month evaluation, two (3%) patients reported worsened IC/BPS, five (8%) patients had no change, and 26 (41%) patients had only mild improvement. Overall, 31 (48%) patients were considered responders and 33 patients were nonresponders (52%); the mean age was similar between the two groups of patients.

At 1 month after the treatment (4 treatments), responders showed significantly lower OSS score, ICSI, ICPI, VAS, daytime urination frequency, and higher GRA than did the nonresponders. At the 6-month evaluation (9 treatments), in addition to OSS score, ICSI, ICPI, VAS, frequency, and GRA, responders showed significantly greater FBC, Q_{max}, and fewer nocturia episodes than did the nonresponders (Fig. 1). The changes in values of parameters from baseline to the 6-month (last) measurement revealed significantly greater changes in OSS score, ICSI, ICPI, VAS, FBC, Q_{max}, and GRA in the responders compared with the nonresponders (Table 2). Although there were 33 nonresponders at 6 months, the changes in OSS score, ICSI, ICPI, and daytime urination frequency from baseline to the 1-month and 6-month evaluations were still statistically significant, suggesting a partial response in these patients.

Table 3 shows the statistical analysis between responders and nonresponders. Only low-grade glomerulations predicted a successful result. The other variables, such as presence of Hunner's lesion, OSS score, VAS, maximal bladder capacity, and daily frequency did not predict the treatment outcome.

During the HA treatment course, 12 episodes of urinary tract infection developed among the 576 instillations (2.1%). No difficult urination, gross hematuria, or large postvoid residual volume was noted. No patient had any systemic adverse event. After the first course of HA treatment, eight (12%) patients remained in good condition without further treatment, 12 (19%) patients continued with the second course of HA treatment because of incomplete symptom relief, 28 (44%) patients shifted to treatment with intravesical botulinum toxin injection, and 16 (25%) patients received oral pentosan polysulfate or other pain treatments.

4. Discussion

The study results confirmed that intravesical HA instillation of one course is an effective treatment for 48.4% of patients with IC/BPS refractory to conventional therapy. Although only some of the patients benefited from the first course of HA treatment, rates of adverse events after HA instillation were low, indicating that HA instillation is safe for IC/BPS treatment.

Treatment of IC/BPS is a considerable challenge to physicians. Previous treatments included oral pentosan polysulfate,[14] intravesical injection of botulinum toxin A,[21] intravesical instillation of chondroitin,[22] and prolonged hydrodistention,[23] but none of these provided long-term treatment success. The adverse events of treatment, for example, the side effects of botulinum toxin-A injection, which include voiding difficulty and painful urination, should be taken into consideration.

Morales et al[10] reported that 71% of IC/BPS patients had positive responses to intravesical HA instillation. Intravesical HA instillation resulted in higher drug concentrations than other treatments and protected the bladder mucosa in patients with IC/BPS. However, not many published studies had such consistent results. Our study showed a lower success rate for one course of HA treatment consisting of four weekly and five monthly instillations. Our patients had chronic IC/BPS and were refractory to conventional therapy. Moreover, the nonresponders had partial responses to the HA treatments, and their IC symptom scores and daytime urination frequency were significantly improved at the 1- and 6-month assessments. However, they did not report a GRA improvement

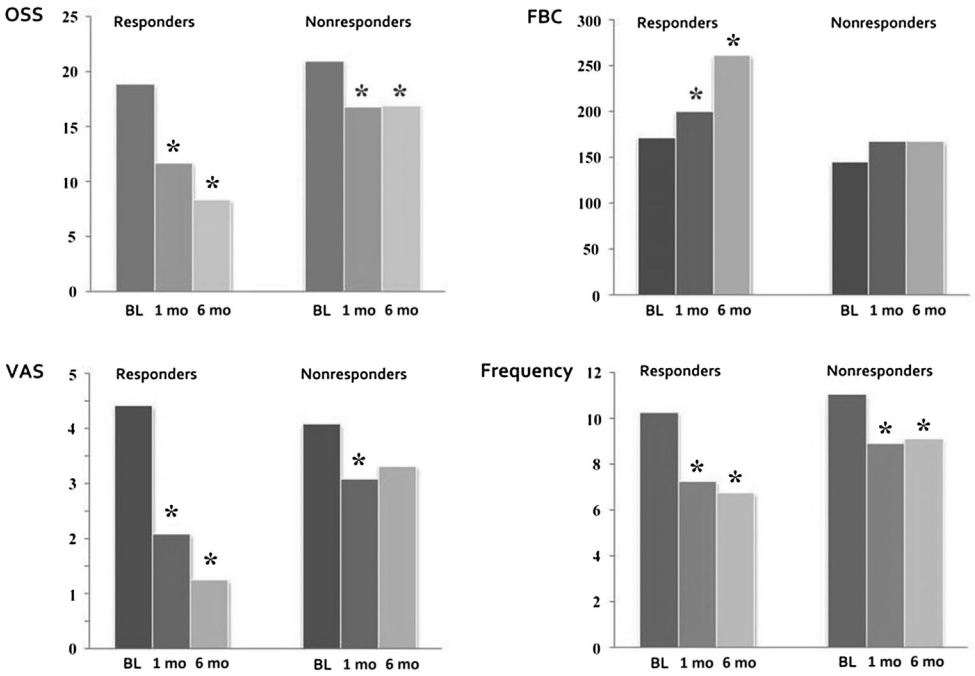

Figure 1. Changes in O'Leary–Sant Symptom (OSS) scores, Visual Analog Scale (VAS) pain score, functional bladder capacity (FBC), and daytime urination frequency from baseline (BL) to 1- and 6-month evaluations between responders and nonresponders. *$p < 0.05$.

Table 2
Changes in values of measured parameters between responders and nonresponders at 1 and 6 months after starting intravesical hyaluronic acid treatment.

		Baseline	1 mo	6 mo	p^*
Age (y)	Nonresponders ($n = 33$)	48.3 ± 12.8	—	—	
	Responders ($n = 31$)	50.5 ± 14.2			
OSS	Nonresponders ($n = 33$)	21.0 ± 6.68	16.8 ± 6.10**	19.7 ± 5.85**	0.001
	Responders ($n = 31$)	18.9 ± 7.88	11.7 ± 5.11**,***	8.39 ± 4.17**,***	
ICSI	Nonresponders ($n = 33$)	10.8 ± 3.46	8.42 ± 3.07**	8.55 ± 3.01**	0.006
	Responders ($n = 31$)	9.87 ± 4.01	6.32 ± 2.45**,***	5.10 ± 2.09**,***	
ICPI	Nonresponders ($n = 33$)	10.2 ± 3.51	8.36 ± 3.44**	8.42 ± 3.20**	< 0.001
	Responders ($n = 31$)	9.03 ± 4.21	5.39 ± 3.18**,***	3.29 ± 2.53**,***	
VAS	Nonresponders ($n = 33$)	4.09 ± 2.16	3.09 ± 2.21**	3.33 ± 2.25	< 0.001
	Responders ($n = 31$)	4.42 ± 2.31	2.10 ± 1.27**,***	1.26 ± 1.00**,***	
FBC (mL)	Nonresponders ($n = 33$)	145 ± 86.7	168 ± 84.4	168 ± 82.2	0.002
	Responders ($n = 31$)	172 ± 94.9	200 ± 90.5**	262 ± 93.3**,***	
Frequency	Nonresponders ($n = 33$)	11.1 ± 4.54	8.94 ± 2.60**	9.12 ± 3.23**	0.213
	Responders ($n = 31$)	10.3 ± 6.35	7.26 ± 2.37**,***	6.77 ± 1.84**,***	
Nocturia	Nonresponders ($n = 33$)	3.30 ± 1.53	2.61 ± 1.20**	2.97 ± 1.26	0.306
	Responders ($n = 31$)	2.90 ± 1.70	2.26 ± 1.12**	2.16 ± 1.27**,***	
Q_{max} (mL/s)	Nonresponders ($n = 33$)	15.8 ± 10.2	15.3 ± 9.60	15.0 ± 6.77	0.037
	Responders ($n = 31$)	16.7 ± 8.93	18.5 ± 8.50	21.1 ± 12.7**,***	
Volume (mL)	Nonresponders ($n = 33$)	227 ± 150	205 ± 121	197 ± 175	0.092
	Responders ($n = 31$)	226 ± 137	247 ± 151	271 ± 153	
PVR (mL)	Nonresponders ($n = 33$)	35.9 ± 38.0	35.5 ± 42.8	33.0 ± 52.8	0.967
	Responders ($n = 31$)	43.1 ± 57.9	37.7 ± 50.8	40.9 ± 62.9	
GRA	Nonresponders ($n = 33$)	—	1.00 ± 0.66	0.73 ± 0.57	< 0.001
	Responders ($n = 31$)	—	2.00 ± 0.68***	2.42 ± 0.50***	

FBC = functional bladder capacity; GRA = global response assessment; ICPI = Interstitial Cystitis Problem Index; ICSI = Interstitial Cystitis Symptom Index; OSS = O'Leary–Sant Symptom score; PVR = postvoid residual volume; VAS = Visual Analog Scale of pain.
* Changes in p values from baseline to 6 months between responders and nonresponders.
** Significant difference in parameters between baseline and time points.
*** $p < 0.05$ between responders and nonresponders.

by $\geq$ 2 scales mostly due to the lack of improvement in VAS and FBC. It is possible that continued HA treatment courses would have improved the success rates.

Studies of urothelial differentiation in IC/BPS patients demonstrated that the acquisition of a transitional cell morphology occurred in some regions of the IC-derived cell lines, suggesting a subset of patients with IC/BPS might have failure of urothelial cytodifferentiation, which could contribute to the disease and bladder dysfunction.[3] Yamada et al[24] demonstrated an apoptotic process in the microvascular endothelial cells of bladders with IC/BPS. A recent study further revealed that urothelial homeostasis in IC/BPS patients was significantly impaired, and the abnormal urothelial function was associated with chronic inflammation of the bladder.[25] Bladder pain and small bladder capacity likely resulted from the defective urothelium and suburothelial inflammation.[26]

A recent prospective, nonrandomized study with 3-year follow up of 20 IC/BPS patients revealed subjective continuing improvement in pain and urination frequency; 11 (55%) patients treated with intravesical HA chose to continue treatment for symptomatic relief.[27] Recent investigation also showed that intravesical HA instillation successfully treated patients with IC/BPS or cyclophosphamide-induced hemorrhagic cystitis.[11–13,28] In the rat immobilization stress model, mean bladder mast cell activation and proinflammatory mediators were inhibited by HA.[29] Using a bladder urothelial cell line, the severity of inflammation based on the release of interleukin-6 after adding tumor necrosis factor-alpha was reduced after treatment with HA and chondroitin sulfate.[30] These clinical results suggest that intravesical HA is potentially effective for bladder inflammation in patients with IC/BPS.

The results of our study also show that higher grade glomerulations significantly lowered success rates compared to patients with low-grade glomerulations. Glomerulation after cystoscopic hydrodistention usually indicates a higher grade of inflammation in the bladder wall. Chronic suburothelial inflammation could inhibit normal basal cell proliferation and affect the apical urothelial function.[31,32] Chronic sensitization of afferent fibers might involve both peripheral and central mechanisms. A rise in bladder nerve growth factor in the muscle or urothelium initiates signals that are transported along the afferent nerves of the bladder to the dorsal root ganglion or spinal cord.[33] Treatment of urothelial dysfunction cannot be solely based on replacement of defense glycoproteins of the bladder urothelium. Based on these data, successful treatment of IC/BPS should target several factors including urothelial defense defects and suburothelial inflammation.

The response to HA treatment was significant only after four instillations and was even more significant after completion of nine instillations among responders. FBC increased in responders only at 6 months, but not at 1 month, suggesting that resolution of bladder inflammation takes more than 1 month to achieve. Weekly HA instillations in the 1st month successfully restored the barrier function to urine solutes; therefore, the VAS and IC symptoms improved. Nonetheless, the bladder inflammation could not be resolved in such a short period of treatment. It is intriguing to note that the three patients with high-grade glomerulations had responses at 1 month, but did not respond to the HA treatment at 6 months. It is possible that the bladder inflammation did not resolve after the 1st month of intensive treatment; therefore, symptoms relapsed when the instillation period increased from weekly to monthly. Based on this observation, we postulate that patients with high-grade glomerulations should be treated more intensely with weekly HA instillation rather than following the conventional treatment regimen.

The main limitation of this study is the lack of a control arm. Because of ethical considerations, it is unconscionable to use a placebo in this specific, vulnerable patient group. Nevertheless, we demonstrated both subjective and objective improvements in Taiwanese responders with IC/BPS, without serious side effects. In addition, all patients had KCl test and urodynamic study performed prior to cystoscopic hydrodistention, and these tests could have caused worsening of their symptoms at baseline. However, the baseline data were obtained 1 month after cystoscopic hydrodistention and at the initiation of HA treatment, and the negative

Table 3
Comparison of the baseline demographics between responders and nonresponders to HA treatment at 6 months.

	Responders ($n = 31$)	Nonresponders ($n = 33$)	p
Sex			0.518
Male	2 (6.5)	1 (3)	
Female	29 (93.5)	32 (97)	
Age (y)			0.808
<30	1 (3.2)	2 (6.1)	
30–50	16 (51.6)	18 (54.5)	
>50	14 (45.2)	13 (39.4)	
ICSI	9.9 ± 4.0	10.8 ± 3.5	0.314
ICPI	9.0 ± 4.2	10.1 ± 3.5	0.239
OSS	18.9 ± 7.9	21.0 ± 6.7	0.254
VAS	4.4 ± 2.3	4.1 ± 2.2	0.558
FBC (mL)			0.386
<100	10 (32.3)	14 (42.4)	
100–250	12 (38.7)	14 (42.4)	
>250	9 (29)	5 (15.2)	
Frequency (per day)			0.395
≤8	5 (16.1)	3 (9.1)	
>8	26 (83.9)	30 (90.9)	
Q_{max} (mL/s)			0.719
<10	7 (22.6)	10 (30.3)	
10–15	7 (22.6)	8 (24.2)	
>15	17 (54.8)	15 (45.5)	
PVR (mL)			0.487
<50	23 (74.2)	22 (66.7)	
50–100	4 (12.9)	8 (24.2)	
>100	4 (12.9)	3 (9.1)	
Hunner's lesion	2 (6.5)	3 (9.1)	0.694
Nonulcer	29 (93.5)	30 (90.9)	
MBC (mL)			0.316
<500	7 (22.6)	11 (33.3)	
500–700	14 (45.2)	9 (27.3)	
>700	10 (32.3)	13 (39.4)	
Glomerulations			0.019
0	3 (9.7)	0	
1	15 (48.4)	11 (33.3)	
2	11 (35.5)	11 (33.3)	
3	2 (6.5)	8 (24.2)	
4	0	3 (9.1)	

FBC = functional bladder capacity; HA = hyaluronic acid; ICPI = Interstitial Cystitis Problem Index; ICSI = Interstitial Cystitis Symptom Index; MBC = maximal bladder capacity; OSS = O'Leary–Sant Symptom score; PVR = postvoid residual volume; Q_{max} = maximum flow rate; VAS = Visual Analog Scale of pain.

impact of the urodynamic study and KCl test was usually absent at that time.

5. Conclusion

Intravesical HA administration improved IC/BPS symptoms, decreased bladder pain, and decreased urination frequency after four instillations, and furthermore decreased nocturia and increased bladder capacity after completion of nine instillations. These results provide evidence supporting the hypothesis that HA has therapeutic effects on patients with IC/BPS, especially those with low-grade glomerulations.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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